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(54) Title: UREA DERIVATIVES HAVING VANILLOID RECEPTOR (VR1) ANTAGONIST ACTIVITY

(57) Abstract: The invention relates to novel compounds having Vanilloid Receptor (VR1) antagonist activity, processes for their preparation, to compositions containing them and to their use in the treatment of various disorders.

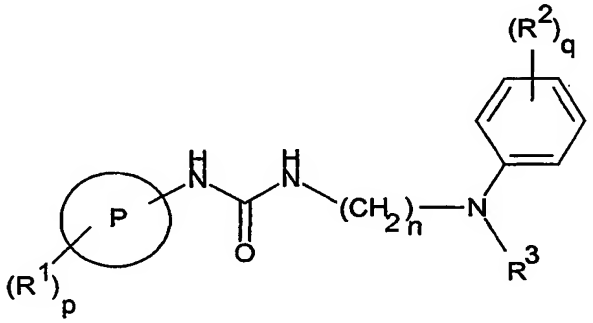
UREA DERIVATIVES HAVING VANILLOID RECEPTOR (VR1) ANTAGONIST ACTIVITY

This invention relates to novel compounds in particular novel urea derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of various disorders.

Vanilloids are a class of natural and synthetic compounds which are characterised by the presence of a vanillyl (3-Hydroxy 4-methoxyphenyl) group or a functionally equivalent group. The vanilloid Receptor (VR1), whose function is modulated by such compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg (The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51, No. 2.).

A wide variety of Vanilloid compounds of different structures are known in the art, for example those disclosed in EP 347000, EP 401903, GB 2226313 and WO 92/09285. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin, namely *trans* 8-methyl-N-vanillyl-6-nonenamide, isolated from the pepper plant, capsazepine (Tetrahedron, Vol. 53, No. 13, pp. 4791- 4814, 1997) and olvanil - N-(3-methoxy-4-hydroxy-benzyl)oleamide (J. Med. Chem. 1993, 36, 2595-2604). Recently, certain vanilloid receptor antagonists have been disclosed in WO02/08221.

A structurally novel class of compounds has now been found which also possess Vanilloid receptor (VR1) antagonist activity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

P is phenyl or naphthyl;

R^1 is halogen, alkyl, CF_3, hydroxy, alkyloxy, CN, OCF_3, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, mono- or dialkylamino or C(O)alkyl;

p is 0, 1, 2 or 3;

n is 2, 3, 4, 5 or 6;

R^2 is halogen, alkyl, CF_3, alkoxy, CN, nitro, aryl, OCF_3, C(O)alkyl, amino, mono- or dialkylamino;

q is 0, 1, 2 or 3;

R^3 is hydrogen, alkyl or arylalkyl.

Suitable alkyl groups are C_{1-6}alkyl groups.

When used herein "alkyl" whether used alone or as part of another group refers to straight chain or branched chain alkyl groups.

The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

The term 'aryl' is used herein to describe, unless otherwise stated, a group such as phenyl or naphthyl. Such aryl groups may be optionally substituted by one or more C_{1-6}alkyl or halogen.

The term 'naphthyl' is used herein to denote, unless otherwise stated, both naphthalen-1-yl and naphthalen-2-yl groups.

When P is naphthyl a preferred group is naphthalen-1-yl. Preferably P is phenyl.

When p is one or more, R^1 is preferably halogen, C_{1-6}alkyl (particularly methyl), C_{1-6}alkoxy (particularly methoxy), C_{1-6}alkylthio (particularly thiomethyl), $C(O)C_{1-6}$alkyl (particularly acetyl), nitro, CF_3, CN or OCF_3.

When p is 2 or 3 the groups R^1 may be the same or different. Preferably p is 1 or 2.

Preferably n is 2 or 3, most preferably 2.

When q is one or more, R^2 is preferably halogen, C_{1-6}alkyl (particularly methyl), C_{1-6}alkoxy (particularly methoxy), CF_3, CN or aryl (particularly phenyl).

When q is 2 or 3 the groups R^2 may be the same or different. Preferably q is 1 or 2. Most preferably q is 1 and R^2 is a methyl group substituted at the 3 position on the phenyl ring.

When R^3 is alkyl, a particularly preferred group is ethyl. When R^3 is arylalkyl preferred groups include benzyl or 2-phenethyl.

A particularly preferred compound of this invention is N-[2-bromophenyl]-N'-[2-(N"-ethyl-N"-(3-methylphenyl)amino)ethyl]urea or a

pharmaceutically acceptable salt thereof. Other preferred compounds of this invention include examples E1, E2, E5, E13, E14, E16, E17, E21, E28, E29 and E30 (as referenced in Table 1 below) or a pharmaceutically acceptable salt thereof.

Suitably, R^1 is halogen.

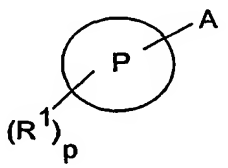
Suitably, R^2 is halogen or alkyl (such as methyl).

The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Compounds of formula (I) may also form solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

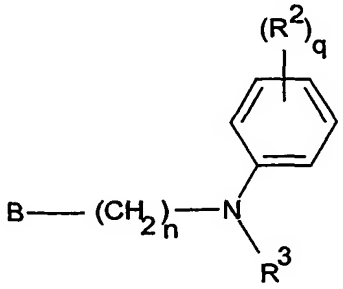
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including diastereomers and enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof.

The present invention also provides, in a further aspect, a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):



(II)

in which R^1, P and p are as defined in formula (I) with a compound of formula (III):



(III)

in which R^2, R^3, n and q are as defined in formula (I) and A and B contain the appropriate functional groups which are capable of reacting together to form the urea moiety; and thereafter carrying out one or more of the following optional steps:

(1) removing any protecting group;

(2) converting R^1 into another R^1 or R^2 into another R^2 or R^3 into another R^3; and

(3) forming a pharmaceutically acceptable salt of a compound of formula (I).

Suitable examples of appropriate A and B groups include:

(a) A is -N=C=O and B is NH_2; or

(b) A is NH_2 and B is NH_2;

(c) A is NH_2 and B is N=C=O.

In process (a) or (c), that is when A is -N=C=O and B is NH_2 or vice versa, the reaction is carried out in an inert solvent such as dichloromethane or acetonitrile.

In process (b) the reaction is preferably carried out in the presence of an appropriate urea forming agent, such as carbonyl diimidazole or phosgene, a suitable solvent being an inert organic solvent such as dimethylformamide, tetrahydrofuran, or dichloromethane at ambient or elevated temperature optionally in the presence of a base such as triethylamine or pyridine.

An alternative method of synthesis of the unsymmetrical urea compounds of formula (I) is from a diaryl carbonate, via the corresponding carbamate. Such a methodology is described by Freer et al. (Synthetic Communications, 26(2), 331 - 349, 1996). It would be appreciated by those skilled in the art that such a methodology could be readily adapted for preparation of the compounds of formula (I).

The above mentioned optional proces steps (1), (2) or (3) are carried out using the appropriate conventional methods, for example those disclosed in standard reference texts such as Comprehensive Organic Transformations, R.C. Larock, Wiley-VCH (Chichester), 1999.

Those skilled in the art will appreciate that it may be necessary to protect certain groups. Suitable protecting groups and methods for their attachment and removal are conventional in the art of organic chemistry, such as those described in Greene T.W. 'Protective groups in organic synthesis' New York, Wiley (1981).

Compounds of formulae (II) and (III) are commercially available or may be prepared according to known methods or analogous to known methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain disorders such as pain, chronic pain,

neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroeosophagal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis and pruritus.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders. In particular the invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof or a solvate thereof for use in the treatment or prophylaxis of chronic and acute pain and urinary incontinence.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral, rectal administration or intravesical adminstration to the bladder and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions, suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

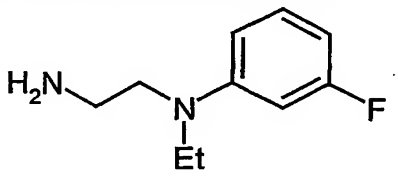
The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01mg to 100mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of the compounds of the invention.

Description 1

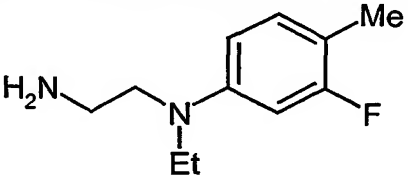
N-ethyl-*N*-(3-Fluorophenyl)ethylenediamine



N-Ethyl-3-fluoroaniline (9.2g, 66mmol) and 2-bromoethylamine hydrobromide (0.5eq.) was heated at reflux in toluene (100ml) for 24h. After cooling solvent was removed under reduced pressure and the residue suspended in diethyl ether (100ml), washed with aqueous potassium carbonate (20% solution, 2x100ml). The ether layer was dried over magnesium sulfate, filtered and solvent removed under reduced pressure. Chromatography on silica gel eluting with dichloromethane and methanol (gradient, maximum 10%) afforded the title compound as an oil (3.9g), MH^+ 183 (100%)

Description 2

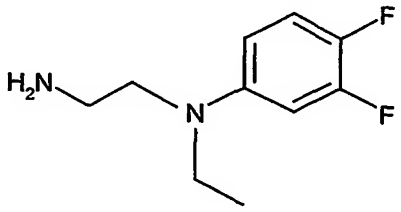
N-ethyl-*N*-(3-Fluoro-4-methylphenyl)ethylenediamine



The title compound was prepared from *N*-ethyl-3-fluoro-4-methylaniline and 2-bromoethylamine hydrobromide according to the procedure outlined in Description 1, MH^+ 197

Description 3

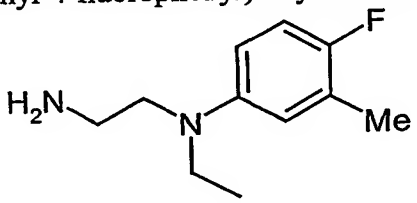
N-ethyl-*N*-(3,4-Difluorophenyl)ethylenediamine



The title compound was prepared from *N*-ethyl-3,4-difluoroaniline and 1-bromoethylamine hydrobromide according to the procedure outlined in Description 1, MH^+ 201

Description 4

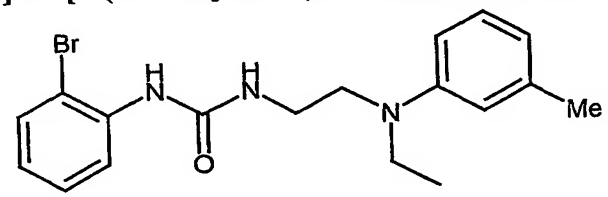
N-ethyl-*N*-(3-Methyl-4-fluorophenyl)ethylenediamine



The title compound was prepared from *N*-ethyl-4-fluoro-3-methylaniline and 2-bromoethylamine hydrobromide according to the procedure outlined in Description 1, MH^+ 197

Example 1

N-[2-Bromophenyl]-N'-[2-(N''-ethyl-N''-(3-methylphenyl)amino)ethyl]urea

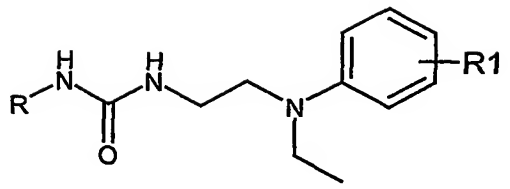


A solution of *N*-ethyl-*N*-(3-methylphenyl)ethylenediamine (TCI, Japan) (0.5g, 2.8mmol) in DCM (3ml) was treated with 2-bromophenylisocyanate (Aldrich) (0.57g, 2.8mmol) in DCM (2ml). After stirring the reaction for one hour at room temperature solvent was removed under reduced pressure to afforded the desired product as an off white solid (0.91g, 86%).

^{1}H NMR (250MHz, $CDCl_3$) δ(ppm): 8.00 (d, 1H), 7.50 (d,1H), 7.26 (m, 1H), 7.10 (m, 1H), 6.92 (m, 1H), 6.55 (m, 4H), 4.95 (br, 1H), 3.47 (m, 4H), 3.37 (q, 2H), 2.30 (s, 3H), 1.14 (t, 3H).

The compounds shown in Table 1 were prepared according to a procedure similar to that of Example E1. All isocyanates used in the synthesis of these Examples are commercially available.

Table 1



Example	R	R1	Observed MH^+
E2	4-F-Ph	3-Me	316
E3	3-CN-Ph	3-Me	323
E4	4-OMe-Ph	3-Me	328
E5	2-Cl-Ph	3-Me	333
E6	3,4-diF-Ph	3-Me	334
E7	3-Ac-Ph	3-Me	340
E8	3-NO_2-Ph	3-Me	341
E9	4-SMe-Ph	3-Me	342
E10	2-Me-3Cl-Ph	3-Me	347
E11	3-Cl-4-F-Ph	3-Me	351
E12	3-Cl-4-Me-Ph	3-Me	347
E13	2-OMe-5-Cl-Ph	3-Me	362
E14	2-OMe-3-Cl-Ph	3-Me	362
E15	3-CF_3-Ph	3-Me	366
E16	2,3-diCl-Ph	3-Me	367
E17	2,5-diCl-Ph	3-Me	367
E18	2-OCF_3-Ph	3-Me	382
E19	2-I-Ph	3-Me	424
E20	1-Naphthyl	3-Me	348
E21	2-Br-Ph	3-F	380
E22	4-F-Ph	3-F	320
E23	2-Cl-Ph	3-F	336
E24	2-Me-3-Cl-Ph	3-F	350
E25	1-Naphthyl	3-F	352
E26	2,3-diCl-Ph	3-F	371
E27	2,5-diCl-Ph	3-F	371
E28	2-BrPh	3-F-4-Me	395
E29	2-BrPh	3,4-diF	399
E30	2-BrPh	3-Me-4-F	395

Pharmacological Data

As referenced above, the compounds of the invention are vanilloid receptor (VR1) antagonists and hence have useful pharmaceutical properties. Vanilloid receptor (VR1) antagonist activity can be confirmed and demonstrated for any particular compound by use of conventional methods, for example those disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W. Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts mentioned herein. The screen used for the compounds of this invention was derived froma FLIPR based calcium assay, similar to that described by Smart et al. (British Journal of Pharmacology, 2000, 129, 227-230).

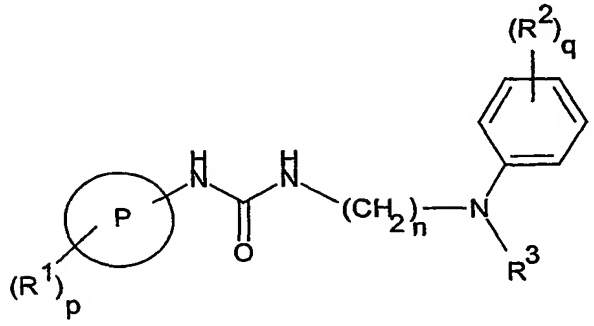
Transfected astrocytoma 1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at 25,000cells/well (96-well plate) and cultured overnight. The cells were subsequently loaded in medium containing 4μM Fluo-3 AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates were then washed 4 times with Tyrode containing 1.5mM calcium, without probenecid.

The cells were pre-incubated with compound or buffer control at room temperature for 30 minutes. Capsaicin (Sigma) was then added to the cells. Compounds having antagonist activity against the human VR1 were identified by detecting differences in fluorescence when measured after capsaicin addition, compared with no compound buffer controls. Thus, for example, in the buffer control capsaicin addition results in an increase in intracellular calcium resulting in fluorescence. A compound having antagonist activity blocks the capsaicin binding to the receptor, there is no signalling and therefore no increase in intracellular calcium levels and consequently lower fluorescence. pKB values are generated from the IC_{50} values using the Cheng-Prusoff equation.

All compounds tested by the above methodology had pKb >6, preferred compounds having a pKb >7.0.

Claims:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

P is phenyl or naphthyl;

R^1 is halogen, alkyl, CF_3, hydroxy, alkyloxy, CN, OCF_3, alkylthio, alkylsulfinyl, alkylsulfonyl, nitro, amino, mono- or dialkylamino or C(O)alkyl;

p is 0, 1, 2 or 3;

n is 2, 3, 4, 5 or 6;

R^2 is halogen, alkyl, CF_3, alkoxy, CN, nitro, aryl, OCF_3, C(O)alkyl, amino, mono- or dialkylamino;

q is 0, 1, 2 or 3;

R^3 is hydrogen, alkyl or arylalkyl.

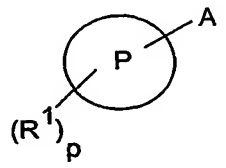
2. A compound according to claim 1 in which P is phenyl.

3. A compound according to claim 1 or claim 2 in which n is 2.

4. A compound according to any of the preceding claims in which R^3 is ethyl.

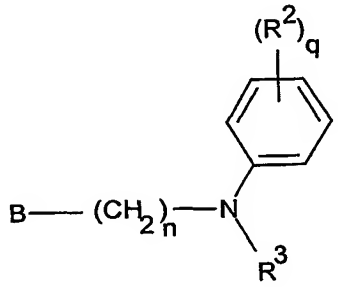
5. A compound according to claim 1 which is:
N-[2-bromophenyl]-N'-[2-(N''-ethyl-N''-(3-methylphenyl)amino)ethyl]urea or a pharmaceutically acceptable salt thereof

6. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises coupling a compound of formula (II):



(II)

in which R^1, P and p are as defined in formula (I) with a compound of formula (III):



(III)

in which R^2, R^3, n and q are as defined in formula (I) and A and B contain the appropriate functional groups which are capable of reacting together to form the urea moiety; and thereafter carrying out one or more of the following optional steps:

(1) removing any protecting group;

(2) converting R^1 into another R^1 or R^2 into another R^2 or R^3 into another R^3; and

(3) forming a pharmaceutically acceptable salt of a compound of formula (I).

7. A compound according to any one of claims 1 to 5 for use in therapy.

8. A compound according to any one of claims 1 to 5 for use in the treatment or prophylaxis of a disorder selected from the list consisting of: pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroeosophagal reflux disorder (GERD),

irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis and pruritus.

9. A method for the treatment or prophylaxis a disorder selected from the list consisting of: pain, chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, migraine, neuropathies, diabetic neuropathy, sciatica, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, inflammatory disorders, oesophagitis, gastroeosophagal reflux disorder (GERD), irritable bowel syndrome, inflammatory bowel disease, pelvic hypersensitivity, urinary incontinence, cystitis, burns, psoriasis, emesis and pruritus, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 5 and a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 02/01046

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C275/40 C07C275/34 C07C275/30 C07C275/32 C07C275/28
C07C323/44 A61K31/17 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 17163 A (YAMANOUCHI PHARMACEUTICAL CO LTD) 30 March 2000 (2000-03-30) page 18; examples 9-2 see also EP1122242 at p.12,l.30-33	1,2,6
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X	DE 39 41 542 A (FUJI PHOTO FILM CO LTD) 28 June 1990 (1990-06-28) page 15; examples III-2	1,2

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 May 2002	05/06/2002

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/01046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X,P	WO 01 82930 A (CHEN XIAOQI ;LI LEPING (US); TULARIK INC (US); CUTLER SERENA T (US) 8 November 2001 (2001-11-08) page 33; example 29 page 34; example 31 page 40; table 1	1-3,6,7, 10
X	CORRAL C ET AL: "JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 14, no. 6, October 1977 (1977-10), pages 985-988, XP002126761 ISSN: 0022-152X page 985; figure 2; examples IVA,IVB	1-3,6
A	US 4 460 602 A (BUCKWALTER BRIAN L ET AL) 17 July 1984 (1984-07-17) column 4 reaction scheme, see in particular the last compound column 13, line 40 -column 14, line 35	1,2,6-10
A	WO 97 11052 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT); SANDOZ PHARMA UK (GB);) 27 March 1997 (1997-03-27) claims 1,10; examples 1,2	1,7,8

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 9 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.

Continuation of Box I.1

Claims Nos.: 9

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna... Application No
PCT/GB 02/01046

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		WO 9711052 A1	27-03-1997

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(54) Title: UREA DERIVATIVES HAVING VANILLOID RECEPTOR (VR1) ANTAGONIST ACTIVITY

(57) Abstract: The invention relates to novel compounds having Vanilloid Receptor (VR1) antagonist activity, processes for their preparation, to compositions containing them and to their use in the treatment of various disorders.

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